## *Remarks*

Claims 25-27, 46, 55, 57-59, and 61-67 are presently pending, with claims 27, 46, and 58 being the independent claims. Claims 63, 66 and 67 are currently withdrawn from consideration on the grounds that they fail to read upon the elected species. Reconsideration of this Application is respectfully requested.

### *I Finality of the Office Action*

Applicants respectfully submit that the finality of the Office Action is premature. According to M.P.E.P. § 706.07(a), second or any subsequent action on the merits shall be final, except where the Examiner introduces a new ground of rejection that is neither necessitated by Applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R. 1.97(c) with the fee set forth in 37 C.F.R. 1.17(p).

Applicants have not filed an information disclosure statement as defined above. The Examiner stated in the outstanding Office Action that Applicants' amendment necessitated the new ground(s) of rejection. Both Gee *et al.* and Bolger *et al.* were cited in an Information Disclosure Statement filed September 8, 1999 and considered by the Examiner on November 19, 1999.

Claim 46 was amended by inserting the phrase "or alkyl" at the end of the second and third provisos. The amendments were initially proposed by the Examiner on May 31, 2000 on a telephone call to the undersigned. However, these amendments did not affect compounds of Formula I wherein $R_3$ is -C(O)-$CH_2$-Y-G where Y is S and G is a C-attached

heteroaryl, now allegedly found obvious over Gee *et al.* Further, the amendments in claim 46 did not affect compounds of Formula I wherein $R_3$ is -C(O)-$CH_2$-O-D where D is a C-attached heteroaryl group, now allegedly found obvious over Bolger *et al.* Furthermore, the amendment to the second proviso did not necessitate the rejection over Bolger *et al.* since the basis for the Examiner's rejection was the substitution in the 17-position by an acetyl derivative (Office Action, page 4, lines 1-2), not the substitution in the 3β-position. Nothing relating to the substitution in the 17-position was amended in response to the previous Office Action. Therefore, it is respectfully submitted that the amendments in claim 46 did not necessitate the new grounds of rejection.

Applicants respectfully request that the finality of the outstanding Office Action be removed as being premature.

***II Rejection under 35 U.S.C. § 103(a) over Gee et al.***

The Examiner has rejected claims 25-27, 46, 55, 57, 59 and 61 under 35 U.S.C. 103(a) as being unpatentable over Gee *et al.*(WO 94/27608). The Examiner states that Gee *et al.* teach compounds and compositions containing 3α-hydroxy pregnan derivatives, such as 3α-hydroxy-21(pyrid-4-ylthio)-5β-prenan-20-one, useful for induction of sleep. According to the Examiner,

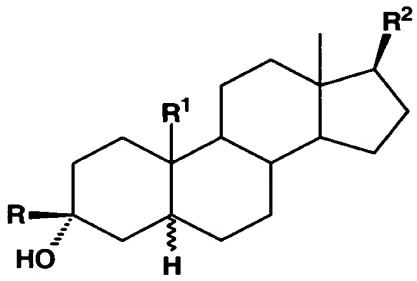
> [t]he instant claims differ from the reference by reciting 3α-hydroxy-21(pyrid-4-ylthio)-5β-prenan-20-one derivatives having a substituent other than hydrogen or alkyl in the 3β-position. However, Gee *et al.* teach substitution in the 3β-position and an equivalence between hydrogen, lower alkyl groups such as methoxymethyl, lower alkynyl groups such as 4-hydroxypent-1-ynyl, (4'-acetylphenyl)ethynyl and ethynyl (see page 11, formula I and lines 9-15). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to make the compound exemplified by Gee

> having any of the above mentioned substituents taught by the prior art with the reasonable expectation that the compound produced would have similar properties as taught by Gee *et al.*

(Office Action at page 3, lines 4-10). Applicants respectfully traverse this rejection.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious, but whether the claimed invention *as a whole* would have been obvious. *See* M.P.E.P. § 2141.02. Thus, a prior art reference must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Gee *et al.* disclose 3α-hydroxy pregnanes of the following formula I:

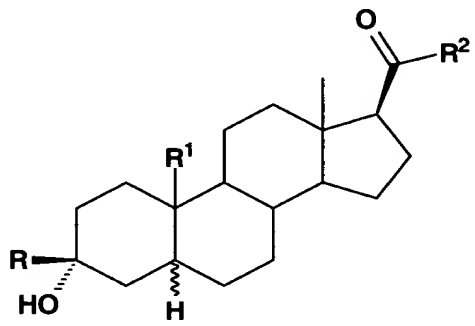



The values of the various substituents on the steroid backbone of Gee's compounds include:

R, the 3β-position, is hydrogen, a lower alkyl group, e.g., methyl and methoxymethyl, a lower alkynyl group, e.g., ethynyl, 4-hydroxypent-1-ynyl and (4'-acetylphenyl)ethynyl, a lower trihaloalkyl group, e.g., trifluoromethyl, a lower monohaloalkyl group, e.g., chloromethyl, a lower alkenyl group, e.g., ethenyl and 2-phenylethenyl, an aryl group, e.g., phenyl, or an aralkyl group, e.g., benzyl.

$R^2$, the 17β-position, is methylene, cyano, hydroxymethyl, methoxymethylene, acetyl, 2'-hydroxyacetyl, 2'-hydroxyacetylacetate, 1-hydroxyethyl, 2'-hydroxyacetyl hemisuccinate, 2'-methoxyacetyl, pyrid-4-ylthioacetyl, ethylene, propylene, 2'-hydroxyacetyl hemisuccinate sodium salt, 1-hydroxybutyl, 1-hydroxy-1-methylethyl, 1-hydroxypropyl, 1-propionyl, 3-methoxypropionyl, ethynyl, 2'-mesyloxyacetyl, or 1'-(ethylenedioxy)ethyl.

The pyrid-4-ylthioacetyl group recited above for $R^2$ appears to be the only group including a heteroaryl group. On page 12, lines 9-25, Gee *et al.* describe a preferred group of compounds of the following formula II:




The values of R and $R^2$ of formula II include:

R, the 3β-position, is a lower alkyl group, e.g., methyl, a lower alkynyl group, e.g., ethynyl, or a trihalo(lower) alkyl group, e.g., trifluoromethyl.

$R^2$, the 21-position, is hydrogen, hydroxy, a pyrid-4-ylthio group, a hemisuccinoyloxy group, or a phosphoryloxy group and the sodium salts thereof.

The definition of the preferred compounds of formula II include three provisos (page 12, lines 14-25). The provisos (1)-(3) read as follows: (1) when R is hydrogen, $R^2$ is a pyrid-4-ylthio group; (2) when $R^1$ is hydrogen, R is a trihalo(lower) alkyl group; and (3) when $R^2$ is

other than hydrogen or a pyrid-4-ylthio group, R is a trihalo(lower) alkyl group. Thus, the provisos (1) and (3) indicate that preferably when $R^2$ is a pyrid-4-ylthio group, the substituent in the 3β-position is hydrogen, and when $R^2$ is other than a pyrid-4-ylthio group, the substituent in the 3β-position is a trihalo(lower) alkyl group. Contrary to the Examiner, Gee *et al.* does not teach the equivalence between hydrogen and other substituents listed above for 3β-position when the 21-position is substituted with a pyrid-4-ylthio group.

Further, the preferred compounds listed on page 13, lines 7-19, include only one compound having a pyrid-4-ylthio group, i.e., 3α-hydroxy-21-(pyrid-4-ylthio)-5β-prenan-20-one. Names for compounds that have been prepared and tested appear in Table 1 of Gee *et al.* Of the hundred compounds listed, only two compounds (the 4th compound on page 75 and the 11th compound on page 76) have a pyrid-4-ylthioacetyl group in the 17β-position, i.e., a pyrid-4-ylthio group in the 21-position. Neither of these two compounds have a substituent other than hydrogen in the 3β-position. Furthermore, Gee *et al.* teach on page 13, lines 4-6, that the preferred compounds of Formula II are those where $R^2$ is a hemisuccinoyloxy group or a phosphoryloxy group, or sodium salt thereof. Thus, Gee *et al.* fails to provide the necessary suggestion to prepare 3α-hydroxy-21-(pyrid-4-ylthio)-5β-prenan-20-one derivatives having other than hydrogen in the 3β-position in order to provide new 3α-hydroxy pregnanes for inducing sleep. Rather, Gee *et al.* teach away from the compounds of the present invention as claimed. Moreover, the first proviso in pending claim 46 provides that the compounds of claim 46 are not even alkylene homologs of the compound described in Gee *et al.* It is respectfully submitted that the claims do not include compounds that are disclosed or fairly suggested by Gee *et al.* Furthermore, Gee *et al.* does not disclose or fairly suggest 3α-hydroxy-2β-propoxy-21-(pyrid-4-ylthio)-5α-pregnan-20-one N-methyl iodide, 3α-hydroxy-

21-(pyrid-4-ylthio)-5α-pregnan-20-one N-methyl iodide, or 3α-hydroxy-21-(pyrid-4-ylthio)-5β-pregnan-20-one N-methyl iodide recited in claim 27.

Reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejection of claims 25-27, 46, 55, 57, 59, and 62 are respectfully requested.

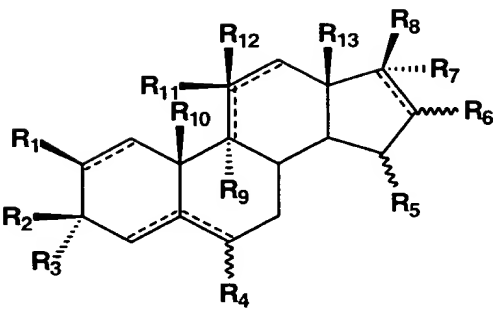
***II Rejection under 35 U.S.C. § 103(a) over Bolger et al.***

The Examiner has rejected claims 25-27, 46, 55, 57-59, 61, and 64-65 under 35 U.S.C. 103(a) as being unpatentable over Bolger *et al.* (U.S. Patent No. 5,232,917). According to the Examiner, Bolger *et al.* teach compounds wherein $R_8$ is $-C(O)-CH_2-O-R_{16}$ and $R_{16}$ is a $C_5$-$C_{10}$ aromatic radical or $C_3$-$C_{10}$ heterocyclic radical (col. 8, lines 5-16). Further, the Examiner states that

> [t]he instant claims differ from the reference by reciting a more limited genus than the reference (i.e. compounds having an acetyl derivative in the 17-position). However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those of the instant claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole. The motivation to make other species taught by Bolger is based on the desire to make additional compounds useful in modulating animal brain excitability via the GABA receptor-chloride complex.

(Office Action at page 3, lines 4-10). Applicants respectfully traverse this rejection.

Bolger *et al.* describe a broad genus of steroid compounds of the formula:




Some of the values of the various substituents on the steroid backbone of Bolger's compounds include:

R1, the 2β-position, can be a number of different substituents, including hydrogen and "a $C_1$-$C_8$ saturated or unsaturated, halogenated or unhalogenated straight chain radical, or $C_1$-$C_8$ saturated or unsaturated, halogenated or unhalogenated branched chain, or $C_3$-$C_8$ cyclic aliphatic radical."

R2, the 3β-position, can be hydrogen, halogen, an ether group or a $C_1$-$C_4$ saturated or unsaturated, halogenated or unhalogenated straight chain radical, or a $C_1$-$C_4$ saturated or unsaturated, halogenated or unhalogenated branched chain radical.

R3, the 3α-position, can be hydroxy.

R7, the 17α-position, can be hydrogen, hydroxyl, halogen, a pharmaceutically acceptable ether -Y-R23, or a $C_1$-$C_4$ saturated or unsaturated, halogenated or unhalogenated straight chain radical, or a $C_1$-$C_4$ saturated or unsaturated, halogenated or unhalogenated branched chain radical.

Y is either a divalent oxygen or sulfur linkage.

R23 is a $C_1$-$C_4$ saturated or unsaturated, halogenated or unhalogenated straight chain radical, or a $C_1$-$C_4$ saturated or unsaturated, halogenated or unhalogenated branched chain radical.

R8, the 17β-position, can be *inter alia*, hydroxyl, thiol, acetyl, 2-hydroxyethanoyl, 1-hydroxyethyl, an ester or thioester, -O-$CH_2$-O-C(O)-R15, -C(O)-R15, or -C(O)-$CH_2$-O-R16, where

R15 is hydrogen, or a $C_1$-$C_{20}$ saturated or unsaturated, halogenated or unhalogenated straight chain radical, or a $C_{1-20}$ saturated or unsaturated, halogenated or unhalogenated branched chain radical, or $C_{3-10}$ cyclic aliphatic radical, or $C_{5-10}$ aromatic radical, or $C_{3-10}$ heterocyclic radical having one ore more 4, 5, 6, or 7 member saturated or unsaturated rings containing 1, 2, or 3 O, N, or S heteroatoms, and

R16 is a $C_{1-10}$ saturated or unsaturated, halogenated or unhalogenated straight chain radical, or a $C_{1-10}$ saturated or unsaturated, halogenated or unhalogenated branched chain radical, or $C_{3-10}$ cyclic aliphatic radical, or $C_{5-10}$ aromatic radical, or $C_{3-10}$ heterocyclic radical having one ore more 4, 5, 6, or 7 member saturated or unsaturated rings containing 1, 2, or 3 O, N, or S heteroatoms or a amide -$(CH_2)_n$-C(O)-N(R15)$_2$.

The general formulae disclosed in Bolger *et al.* contain a very large number of variables. The basic structure at column 5 includes 13 "R" groups, a number of which themselves are defined by reference to still further variable R, X, Y and A groups. In addition, the structure allows the presence of either a single bond or a double bond at six different locations in the steroid system. The variation in the first six variables $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, and $R_6$ easily accounts for more than a billion different compounds. Thus the generic formula of Bolger *et al.* encompasses a potentially infinite genus of 3α-hydroxy steroid derivatives.

It is possible to construct a steroid compound having an acetyl derivative as claimed in the present invention in the 17β-position by picking and choosing from among the myriad of possibilities allowed by the Bolger *et al.* genus. However, nothing in Bolger *et al.* provides any guidepost for choosing a compound that has a 17β-C(O)-$CH_2$-O-R16 group where R16 is an optionally substituted aryl group or a C-attached heteroaryl group according to the present invention. *See, In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Structures for preferred compounds that had been synthesized and tested appear in Table 2 of Bolger *et al.* Of the twenty-nine compounds listed, no compounds have the 17β-C(O)-$CH_2$-O-R16 group as claimed in the present invention. It is respectfully submitted that the claims do not include compounds that are disclosed or fairly suggested by Bolger *et al.*

Reconsideration and withdrawal of the 35 U.S.C. § 103(a) rejection of claims 25-27, 46, 55, 57-59, 61, and 64-65 are respectfully requested.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

No amendments are made to the application. Thus, this Reply does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since

all of the elements and their relationships claimed were earlier claimed. Therefore, this Reply should allow for immediate action by the Examiner.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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